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Controlled release and biocompatibility of polymer/titania nanotube array system on titanium implants

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ABSTRACT

Bacterial infection and tissue inflammation are the major causes of early failure of titanium-based orthopedic implants; thus, surgical implants with tunable drug releasing properties represent an appealing way to address some of these problems of bacterial infection and tissue inflammation in early age of orthopedic implants. In this work, a hybrid surface system composed of biodegradable poly(lactic-co-glycolic acid) (PLGA) and titania nanotubes (TNTs) has been successfully constructed on Ti implants with the aim of preventing bacterial infection via long-term drug release. By varying the size of the TNTs and the thickness of the polymer film, the drug release profile can be tuned to achieve the optimal therapeutic action throughout the treatment time. The size of TNTs plays a dominant role in the drug loading dose of TNTs/PLGA hybrid coatings. In this work, TNTs with an average size of 80 nm can achieve the largest loading dose. Depending on the polymer thickness, significant improvement in the drug release characteristics is attained, for instance, reduced burst release (from 84% to 27%) and overall release time extended from 5 to over 40 days. In addition, the PLGA layers may favor the proliferation and osteogenesis of MC3T3-E1 mouse cells at an earlier stage. Therefore, this TNT/PLGA hybrid surface system can be employed as an effective bioplatform for improving both self-antibacterial performance and biocompatibility of Ti-based biomaterials.
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1. Introduction

Titanium (Ti) and titanium alloys are used in orthopedic implants because of their desirable mechanical strength, corrosion resistance, and biocompatibility [1,2]. However, implant failure arising from post-surgery infection remains one of the most serious complications after surgery [3,4]. Although antibiotics are usually prescribed to prevent complications [3], systemic drug administration, regardless of whether it is intravenous, intramuscular, or topical, suffers from limitations such as low drug solubility, poor biodistribution, lack of selectivity, uncontrolled pharmacokinetics, and serious side effects on non-target tissues [5]. Hence, surface modification, including building a local antibacterial agents delivery system to the implantation site, is preferred [6,7]. Vancomycin, penicillin, gentamicin, antimicrobial peptides, and indomethacin have been used as drugs for this purpose because they mitigate inflammation and inhibit bacteria growth [8–10].

Titanium dioxide (TiO_2) has attracted much attention since the discovery of its excellent photocatalytic performance in water splitting when illuminated by ultraviolet (UV) light [11–13], and extensive research on the fabrication, structure, and application of TiO_2 nanomaterials has ensued [14,15]. In 1999, Zwilling and co-

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workers found that TiO_2 porous membranes could be produced on Ti by anodic oxidation in a fluoride electrolyte [16], and in 2001, Gong et al. reported the preparation of even and orderly TiO_2 nanotubes (TNTs) on Ti by anodic oxidation in an electrolyte containing hydrofluoric acid (HF) [17]. Since then, uniform TNT arrays with various pore sizes (22–110 nm), lengths (200–6000 nm), and wall thicknesses (7–34 nm) have been produced by adopting different conditions [18,19]. Due to the low immunogenicity of TNT arrays, they are introduced into biological applications [20]. TNT arrays have also been reported to have the ability to direct stem cell fate [21] and regulation of the behavior of endothelial cells. Furthermore they also can improve osteoblast attachment, function, and proliferation [22–24]. In addition, targeted delivery of antibiotics and drugs from TNTs has been studied [25–29]. However, the connection between TNT size and the dose of loaded drugs has not previously been investigated very deeply.

Alleviating pain and reducing inflammation after surgeries are important. Ibuprofen, a nonsteroidal chemical, is used as an analgesic, antipyretic, and anti-inflammatory drug. However, it has a fairly short action time because of a limited half-life of only 1–3 h, thus requiring frequent oral or parenteral administration [30]. Ibuprofen release time must therefore be prolonged; the use of a polymer coating to control the elution kinetics of ibuprofen is the main objective of this piece of work. In this work, TNT arrays are produced on Ti in an ethylene glycol electrolyte containing ammonium fluoride, and poly (lactic-co-glycolic acid) (PLGA), a biodegradable and antibacterial polymer [31,32], is coated onto the TNT arrays. Additionally, PLGA has been reported to have good biocompatibility for cell attachment and proliferation [33]. The effects of the thickness of the PLGA layer on the release behavior of ibuprofen from coatings are explored and discussed. Furthermore, the biocompatibility of samples is explored via *in vitro* test.

2. Experimental section

2.1. Materials

Titanium disks (99.6% Ti) with a thickness of 0.25 mm and diameter of 6 mm were supplied by Baosteel Group Corp (Shanghai, China). Ethylene glycol (EG) and ammonium fluorides (NH_4F) were obtained from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). The poly (D, L-lactide-co-glycolide) (PLGA) co-polymer with a molar ratio of LA:GA of 75:25 and low molecular weight with an inherent viscosity of 0.61 dL/g was provided by Daigang BIO Engineer Limited Co. (Jinan, China). Ibuprofen was purchased from Zhengzhou Sainuokang Chemical Products Co., Ltd. (China).

2.2. Synthetic methods

2.2.1. Fabrication of TNT arrays on Ti

The Ti disks were cleaned by acetone, ethanol, and deionized water using an ultrasonic cleaner. Then they were etched in solution containing HF, HNO_3, and H_2O at a ratio of 1:4:5 [34]. TNT arrays were synthesized by a two-electrode DC anodization system. The electrolyte contained 0.3% NH_4F, ethylene glycol, and H_2O with volume ratio of 3:97 between ethylene glycol and water. The effects of the reaction temperature, anodization voltage, reaction time and gravity on the microtopography of the TNTs were studied. The anodization voltage was varied from 10 to 60 V, reaction time from 10 to 180 min, and reaction temperature from 0 to 100 °C.

2.2.2. Drug loading and release study

In order to aviod capillarity, the prepared TNTs were cleaned by deionized water and dried in vacuum oven at 60 °C for 24 h, and then they were immersed in ibuprofen solution (100 mg/mL) for 2 days [35].

The PLGA solution of chloroform was then prepared. The concentrations of PLGA solution [0.5%, 1%, and 2% (w/v)] was pipetted onto the drug loaded TNTs, spin coated, and dried in air. The steps were repeated if necessary.

The amount of drug release from TNT/PLGA samples was determined using ultraviolet–visible (UV–Vis) spectrophotometry [36]. UV–Vis measurements were taken at short intervals during the first 6 h after preparation to monitor the initial burst release of ibuprofen, followed by testing every 24 h to observe the long-term release behavior until all the drug had been released to the phosphate buffered solution (PBS). The percentage of drug release was calculated by dividing the accumulated amount of released drug by the total loaded amount. The total amount of drug loading was detected when the UV–Vis absorption spectra exhibited no further changes.

2.3. In vitro study

2.3.1. Cell viability

The MTT (3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyl tetrazolium bromide) assay could be used to determine the cell viability of the samples. First, 350 μL 1×10^5 mL^{-1} mouse MC3T3-E1 cells (Tongji Hospital, Wuhan, China) were cultured at 48-well plate with samples at the bottom at 37 °C in a humidified atmosphere of 5% CO_2 for 1, 3, and 7 days. After removing the medium, 350 μL MTT (0.5 mg/mL) solution was dissolved into the sterilized PBS (pH 7.4), and then incubated in a 5% CO_2 incubator for 4 h. After incubation, the medium was removed and 350 μL dimethyl sulfoxide (DMSO) was added into the well, followed by incubation of the color reaction for 15 min in an incubator. After that, the samples were removed and the cultured medium was measured by the microplate reader at wavelengths of 490 nm and 570 nm. The cell viability is determined from the absorbance readings and calculated by dividing the values of samples to those of the control.

2.3.2. Alkaline phosphatase activity

An alkaline phosphatase (ALP) assay was used to determine the osteogenic differentiation on the samples after culturing for 3, 7, and 14 days. After incubation at 48-well plate with samples at the bottom at 37 °C in a humidified atmosphere of 5% CO_2, the medium was removed and 500 μL of Triton X-100 (1%) was added into the 48-well plates. After shaking 5 min, the 48-well plate with samples was incubated in a water bath at 37 °C for 1 h. Then, 30 μL supernatant was tested by using an AKP ELISA kit at the wavelength of 520 nm by the microplate reader.

2.3.3. Cell morphology

Mouse MC3T3-E1 cells (1×10^4 cell/mL) were seeded into the 48-well plates containing pre-sterilized samples. After 8 h of incubation at 37 °C in a humidified atmosphere of 5% CO_2, samples were washed with PBS (37 °C) three times and then samples were immersed into a 4% formaldehyde solution for 10 min. After that, samples were washed with PBS an additional three times. Subsequently, the samples were immersed in FITC (YiSen, Shanghai, China) for 30 min in the absence of light at room temperature, and then washed with PBS three times. The samples were then successively stained with DAPI (YiSen, Shanghai, China) at room temperature in the dark for just 30 s. After washing with PBS three additional times, the cell morphology was examined using an inverted fluorescence microscope (IFM, Olympus, IX73).

3. Results and discussion

3.1. Characterization

The structure and morphology of the TNTs can be controlled by

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